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Clinical Research

Different Prognostic Significance of High On-Treatment Platelet Reactivity as Assessed by the VerifyNow P2Y12 Assay After Coronary Stenting in Patients With and Without Acute Myocardial Infarction

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Objectives This study compared the prognostic role of high on-treatment platelet reactivity (HTPR) in predicting thrombotic events in a Korean population undergoing percutaneous coronary intervention (PCI) in the acute myocardial infarction (AMI) and non-AMI setting.

Background The prognostic significance and optimal cutoff of HTPR might differ according to a given clinical condition, such as AMI and ethnicity.

Methods On-treatment platelet reactivity was measured with a VerifyNow P2Y12 assay (Accumetrics, San Diego, California) in 1,226 patients (824 men; age 65 ± 10 years), including 413 AMI cases, 12 to 24 h after PCI between March 2008 and March 2010. The prevalence of cardiovascular (CV) events defined as a composite of death from CV causes, nonfatal myocardial infarction, or stent thrombosis at 1-year follow-up were compared according to HTPR between patients with and without AMI.

Results The optimal cutoff for HTPR was 272 IU of the $P2Y_{12}$ reaction unit (PRU) (area under the curve: 0.708; 95% confidence interval [CI]: 0.607 to 0.809, $p = 0.03$), which was the upper-tertile threshold. Among AMI patients, 1-year CV events occurred more frequently in patients with versus without HTPR (n = 14 [8.8%] vs. n = 1 [0.4%], $p < 0.001$), whereas there was no difference in the composite endpoint on the basis of HTPR in patients without AMI (n = 7 [2.8%] vs. n = 8 [1.4%], $p = 0.193$).

Conclusions Increased residual platelet reactivity is related to post-discharge CV events in subjects with AMI, whereas the prognostic significance of HTPR seems to be attenuated in patients with stable coronary disease after PCI. (J Am Coll Cardiol Intv 2012;5:259–67) © 2012 by the American College of Cardiology Foundation

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The response to clopidogrel varies considerably, due to several mechanisms, including absorption and hepatic conversion to its active metabolite (1). High on-treatment platelet reactivity (HTPR) to adenosine diphosphate has been found to be a predictor of major adverse cardiovascular (CV) events, such as death from CV causes, nonfatal myocardial infarction (MI), and stent thrombosis in patients with coronary artery disease (CAD) after percutaneous coronary intervention (PCI) (2–5). The numerous studies (2,5–7) with the VerifyNow P2Y12 assay (Accumetrics, San Diego, California) showed a concrete association between HTPR and thrombotic events. The optimal cutoff values for HTPR ranged between 230 and 240 IU of the $P2Y_{12}$ reaction unit (PRU) among studies, which were approximately upper-tertile values (2,5–7). An expert group suggested a similar cutoff value for HTPR (8).

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Abbreviations and Acronyms

AMI = acute myocardial infarction
CAD = coronary artery disease
CI = confidence interval
CV = cardiovascular
DM = diabetes mellitus
HR = hazard ratio
HTPR = high on-treatment platelet reactivity
PCI = percutaneous coronary intervention
PRU = $P2Y_{12}$ reaction unit
ROC = receiver-operating characteristic

We hypothesized that the prognostic role and cutoff of HTPR might differ according to a given clinical condition, such as acute myocardial infarction (AMI), ethnicity, and sampling time. Therefore, we aimed to evaluate whether the prognostic role of HTPR as assessed with the VerifyNow P2Y12 assay differs between AMI and non-AMI settings. We also sought to investigate the optimal cutoff for HTPR in predicting CV events in Korean subjects undergoing PCI.

Methods

The study protocol was approved by the Ethical Review Board of Wonju College of Medicine, Yonsei University (Wonju, South Korea). Informed consent was obtained from all participants.

Study population. Clinical, laboratory, and angiographic data were collected consecutively and prospectively in 1,650 subjects who underwent PCI with drug-eluting stents at Wonju Christian Hospital between March 2008 and March 2010. One hundred forty-seven patients did not consent to participate in the study. Eighteen patients died during the procedure or the hospital stay before the VerifyNow P2Y12 assay was carried out. Eighty-three patients concomitantly received glycoprotein IIb/IIIa inhibitors. One hundred thirty-one patients did not have platelet function tests. Other exclusion criteria were contraindications for antiplatelet therapy, previous use of anticoagulants, severe left ventricular dysfunction (ejection fraction <30%), cardiogenic shock, neoplastic disease, platelet count <150,000/ml, and hemoglobin <10 g/l. Thus, the total study cohort comprised 1,226 subjects, including 413 patients with AMI (186 non–ST-segment elevation MI and 227 ST-segment elevation MI) (Fig. 1).

Coronary angiography and antithrombotic regimens. All patients received aspirin (300 mg) and clopidogrel (600 mg) before the start of the coronary procedure. A bolus of unfractionated heparin (70 U/kg) was administered immediately before PCI. The PCI was undertaken via a transradial or transfemoral approach with conventional methods with balloon pre-dilation followed by drug-eluting stent deployment. In AMI cases, aspiration thrombectomy was used at the discretion of the operator. Aspirin (100 mg) and clopidogrel (75 mg) were given for ≥12 months after PCI. Giving cilostazol in addition to dual antiplatelet therapy was permitted, depending on the preference of the clinician only after the platelet function assay.

Blood sampling and the VerifyNow P2Y12 assay. Blood samples were obtained 12 to 24 h after PCI. Irrespective of prior exposure to clopidogrel, 600 mg was administered before PCI. Each sample was placed in a tub containing 3.2% citrate, and the PRU was assessed within 2 h with the VerifyNow P2Y12 test as previously described (9). The HTPR was defined as ≥272 PRU. This cutoff was chosen because it was: 1) the upper-tertile value in the study cohort; and 2) similar to those used in the receiver-operating characteristic (ROC) curve analysis to identify HTPR for the prediction of CV events in Korean patients with CAD (10–13).

Main outcome measures. The primary endpoint was the 1-year prevalence of the composite of death from CV causes, nonfatal MI, or stent thrombosis. All deaths were considered CV unless an unequivocal non-CV cause could be confirmed. Myocardial infarction was defined according to criteria set by the American College of Cardiology (14) as a rise in serum troponin I or an increase in creatine kinase-myocardial band isoenzyme at least twice the upper normal limits with at least 1 of the following: acute onset of prolonged (≥20 min) typical ischemic chest pain; ST-segment elevation of at least 1 mm in 2 or more contiguous electrocardiographic leads or ST-segment depression ≥0.5 mm in ≥2 contiguous leads; or T-wave inversion >1 mm in leads with predominant R waves. Stent thrombosis was defined as "definite" or "probable" according to definitions set by the Academic Research Consortium (15).

Statistical analyses. Continuous variables are presented as mean ± SD or median (intertertile range), and categorical variables are presented as frequencies (percentage). Continuous variables were compared with the Student *t* test. The chi-square test or Fisher exact test were used if the expected cell count was <5 for a 2 × 2 table for categorical variables. The ROC analyses were used to determine the ability of the PRU to discriminate between patients with and without

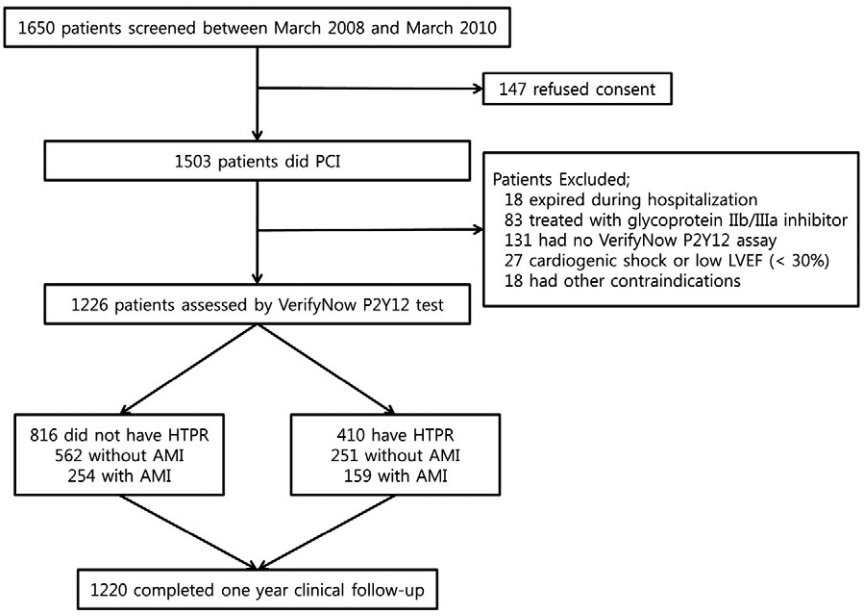

Figure 1. Study Flow Chart

The diagram shows process of the present study. AMI = acute myocardial infarction; HTPR = high on-treatment platelet reactivity; LVEF = left ventricular ejection fraction; PCI = percutaneous coronary intervention.

post-discharge CV events after PCI. The upper-tertile PRU value (272) was determined as the optimal cutoff for HTPR that provided reasonably high sensitivity (70%) and high specificity (68%). Survival curves for patients with and without HTPR were generated by the Kaplan–Meier method and compared with the log-rank test. The aforementioned analyses were undertaken separately in patients with and without AMI. After assessment of the proportional hazard assumption, the Cox regression model for univariate and multivariate analyses were used, respectively, to identify risk factors for outcome and to adjust for potential confounders associated with endpoints upon univariate analysis (age, sex, diabetes mellitus [DM], chronic kidney disease, C-reactive protein level ≥3 mg/l, AMI setting, HTPR, reduced left ventricular ejection fraction, multivessel disease, total length of stent and bifurcation lesions). A p value <0.05 was considered significant. All analyses were carried out with SPSS (version 17.0, SPSS, Chicago, Illinois).

Results

Between March 2008 and March 2010, 1,226 patients were screened with platelet function testing 12 to 24 h after PCI. Of these, 410 patients had HTPR (Fig. 1). Baseline clinical, lesion, and procedural characteristics according to HTPR are summarized in Table 1. Patients with HTPR were older (67 ± 11 years vs. 62 ± 11 years, $p < 0.001$) and less likely to be men (50.2% vs. 75.5%, $p < 0.001$). The presence of DM or hypertension, being a current smoker, having previously undergone PCI or coronary artery bypass grafting, and renal insufficiency were not associated with HTPR. The prevalence of concurrent use of medications between the 2 groups was quite similar, except for statins (which were taken less frequently by patients with HTPR). The number of vessels treated/patient was higher (1.9 ± 0.8 vs. 1.8 ± 0.8, $p = 0.013$) and the mean diameter of the stent was smaller in patients with HTPR (3.20 ± 0.47 mm vs. 3.28 ± 0.48 mm, $p = 0.003$). Higher mean on-treatment platelet reactivity was observed in patients with versus those without AMI (241 ± 94 PRU vs. 229 ± 83 PRU, $p = 0.018$).

Outcomes at 1 year in patients stratified by post-clopidogrel platelet reactivity. Clinical follow-up at 1 year was complete in 1,220 (99.5%) participants. After discharge, there were 30 patients with CV events (2.4%), including 18 CV deaths (1.5%), 16 nonfatal MI (1.3%), and 19 episodes of stent thrombosis (1.6%). Patients with adverse events had significantly higher on-treatment platelet reactivity than those who did not experience events (290 ± 84 PRU vs. 232 ± 86 PRU, $p < 0.002$). Patients with HTPR had a significantly greater prevalence of CV mortality (14 [3.4%] vs. 4 [0.5%], $p < 0.001$) and stent thrombosis (13 [3.2%] vs. 6 [0.7%], $p < 0.001$) and a combined endpoint of CV death, nonfatal MI, or stent thrombosis (21 [5.1%] vs. 9 [1.1%], $p < 0.001$). There was no difference concerning the prevalence of

Table 1. Baseline Clinical and Procedural Characteristics of Study Patients on the Basis of HTPR

	No HTPR (n = 816)	HTPR (n = 410)	p Value
Residual platelet reactivity, PRU	185 ± 60	328 ± 43	<0.001
Age yrs	62 ± 11	67 ± 11	<0.001
Men	618 (75.5)	206 (50.2)	<0.001
Body mass index, kg/m^2	24.9 ± 3.3	24.8 ± 3.2	0.777
Medical history			
Diabetes mellitus	267 (32.7)	132 (32.2)	0.853
Hypertension	493 (60.3)	254 (62.08)	0.575
Hyperlipidemia	265 (32.5)	128 (31.0)	0.657
Current smoker	257 (31.5)	123 (30.0)	0.602
Prior MI	35 (4.3)	16 (4.0)	0.598
PCI	81 (9.9)	49 (12.0)	0.277
CABG surgery	3 (0.4)	2 (0.5)	0.755
Renal insufficiency	31 (3.8)	14 (3.4)	0.685
Concomitant medication			
Beta-blocker	620 (76.0)	325 (79.3)	0.315
Calcium-channel blocker	159 (19.5)	67 (16.3)	0.186
ACE inhibitor or ARB	537 (65.8)	291 (71.0)	0.135
Statin	612 (75.0)	271 (66.1)	0.001
Proton pump inhibitor	43 (5.3)	25 (6.1)	0.550
Cilostazol	105 (12.9)	67 (16.3)	0.097
Indication for procedure			0.022
Stable angina or unstable angina without elevated cardiac enzymes	562 (68.9)	251 (63.5)	
NSTEMI	117 (14.3)	69 (16.1)	
STEMI	137 (16.8)	90 (20.4)	
Left ventricular ejection fraction, %	55 ± 13	57 ± 48	0.360
Procedural variables			
Vessels/patient	1.8 ± 0.8	1.9 ± 0.8	0.013
Stents/patient	1.7 ± 0.9	1.7 ± 0.8	0.994
Total stent length, mm	42 ± 24	43 ± 24	0.733
Stent diameter, mm	3.28 ± 0.48	3.20 ± 0.47	0.003
Left main lesion	28 (3.4)	11 (2.7)	0.481
Bifurcation lesion	125 (15.3)	66 (16.1)	0.723

Values are n (%) or mean ± SD.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CABG = coronary artery bypass surgery; HTPR = high on-treatment platelet reactivity; MI = myocardial infarction; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PRU = $P2Y_{12}$ reaction unit; STEMI = ST-segment elevation myocardial infarction.

nonfatal MI between the 2 groups (8 [1.0%] vs. 8 [2.0%], p = 0.158). Table 2 demonstrates the prevalence of events between patients with and without HPR as stratified by AMI status. Among patients without AMI, no difference in the prevalence of events was found between the 2 groups, whereas composite CV events occurred more frequently in patients with HTPR than in those without HTPR in the AMI group (8.8% vs. 1.6%, p < 0.002). Patients with AMI and HTPR had a higher prevalence of CV death (6.9% vs. 0.7%, p < 0.001) and stent thrombosis (4.4% vs. 0%, p = 0.001) than those without HTPR.

The event-free survival curves for the combined endpoint of CV events according to the presence of HTPR are shown in Figure 2. One-year survival free from the combined endpoint of CV death, nonfatal MI, or stent thrombosis was 94.9% in patients with HTPR and 98.9% in patients without HTPR (Fig. 2A) (p < 0.001). Among patients without AMI, no differences in event-free survival were found according to the presence of HTPR (Fig. 2B) (p = 0.196), whereas patients with AMI and HTPR had a higher prevalence of events than those without HTPR (Fig. 2C) (p < 0.001).

Only 172 patients (14%) received cilostazol in the present population. There was no significant difference in clinical outcome according to use or no use of cilostazol (3.5% vs. 2.1%, p = 0.256).

Platelet reactivity and ROC curve analyses. The PRU was unimodally distributed (1-sample Kolmogorov–Smirnov test, p = 0.236) with mean value of 232 ± 87 (intertertile

Table 2. 1-Year CV Events According to Clopidogrel Response, Stratified by AMI and HTPR

	No AMI (n = 813)			AMI (n = 413)		
	No HTPR (n = 562)	HTPR (n = 251)	p Value	No HTPR (n = 254)	HTPR (n = 159)	*p* Value
All CV events	8 (1.4)	7 (2.8)	0.193	1 (1.6)	14 (8.8)	<0.001
CV death	3 (0.5)	3 (1.2)	0.383	1 (0.7)	11 (6.9)	<0.001
Nonfatal MI	7 (1.2)	3 (1.2)	1.000	1 (0.7)	5 (3.1)	0.031
Stent thrombosis	6 (1.1)	6 (2.4)	0.158	0 (0)	7 (4.4)	0.001

Values are n (%).
CV = cardiovascular; other abbreviations as in Table 1.

range 194 to 272). A ROC curve analysis of PRU could be used to distinguish between patients with and without subsequent CV events (area under the curve: 0.708, 95% confidence interval [CI]: 0.607 to 0.809, $p < 0.001$). If divided between those with or without AMI, the area under the curve was larger in patients with AMI (0.792, 95% CI: 0.708 to 0.876, $p < 0.001$) compared with those without AMI (0.601, 95% CI: 0.433 to 0.769, $p = 0.180$) (Fig. 3). A PRU ≥272 was identified as the optimal cutoff value to predict post-discharge 1-year outcomes, providing a sensitivity of 70% and specificity of 68%. In AMI patients, HTPR defined as PRU ≥272 had a sensitivity of 93% and specificity of 65%. Conversely, in non-AMI patients, HTPR could not be used to distinguish between patients with and without CV events.

Upon multivariate Cox regression analysis, HTPR was associated with a significantly higher risk of CV death (hazard ratio [HR]: 7.352, 95% CI: 1.522 to 35.515, $p = 0.013$) and the combined endpoint of CV events (HR: 3.749, 95% CI: 1.400 to 10.04, $p = 0.009$) after adjusting for potential confounders that were associated with endpoints on univariate Cox regression analysis (age, sex, DM, chronic kidney disease, ≥3 mg/l of C-reactive protein, <45% of ejection fraction, AMI setting, multivessel disease, total stent length, and bifurcation lesions) There was a nonsignificant trend toward greater risk of stent thrombosis in those with HTPR (HR: 2.833, 95% CI: 0.933 to 8.913, $p = 0.066$). Low ejection fraction (<45%), elevated creatinine level (≥1.5 mg/dl), and HTPR were independent predictors for 1-year combined endpoint of CV events (Table 3).

Discussion

The main finding of the present study was that HTPR defined as ≥272 of PRU provided valuable prognostic information in patients with AMI but that its prognostic significance was attenuated in the non-AMI setting.

Numerous studies (2–5) have demonstrated an association between increased residual platelet reactivity and subsequent adverse outcome. Hence, individualized therapy according to HTPR has attracted the attention of many researchers (16–18). Finally, the GRAVITAS (Gauging Responsiveness with A VerifyNow assay–Impact on Thrombosis And Safety) trial aimed to determine the benefit of tailoring antiplatelet therapy with double-dose clopidogrel in patients with HTPR but failed to demonstrate improved outcome (7). Possible explanations of the negative results are the relatively low-risk CAD patients included; insufficiency of double-dose clopidogrel to overcome HPR; and a lower prevalence of clinical events (2.3% in both groups). That finding corresponds well with our result of no differences in outcomes between patients with and without HPR in the non-AMI setting. In line with this observation, the TRIGGER-PCI (Testing Platelet Reactivity in Patients Undergoing Elective Stent Placement on Clopidogrel to Guide Alternative Therapy With Prasugrel) trial, which assessed outcomes in patients with HTPR undergoing elective PCI randomized to prasugrel or clopidogrel, was recently halted due to the low prevalence of events. The prognostic significance of HTPR on thrombotic events might be attenuated in patients with stable CAD after PCI because of the lower prevalence of events. This negative finding of HTPR in non-AMI cohort might be due to underpowering, because the proportion of all CV events in HTPR group (2.8%) was still twice as high as those in no HTPR group (1.4%). A large-size trial involving approximately 1,723 subjects with stable coronary disease would be required to achieve adequate power to show whether HTPR is beneficial in predicting midterm post-discharge CV risk (at $p < 0.05$ both side, power = 0.8).

Conversely, in the AMI subgroup, CV events occurred more frequently in patients having HTPR. Thus, new strategies (e.g., more potent antiplatelet agents or adding cilostazol to standard dual-antiplatelet therapy) might be needed to overcome HTPR in settings such as AMI, which enhances platelet reactivity. Cilostazol had no impact on decreasing thrombotic events in this study. Because only 14% of patients received cilostazol and the present study was not designed to investigate the clinical impact of cilostazol, further research is warranted to assess clinical benefit of cilostazol in patients with HTPR.

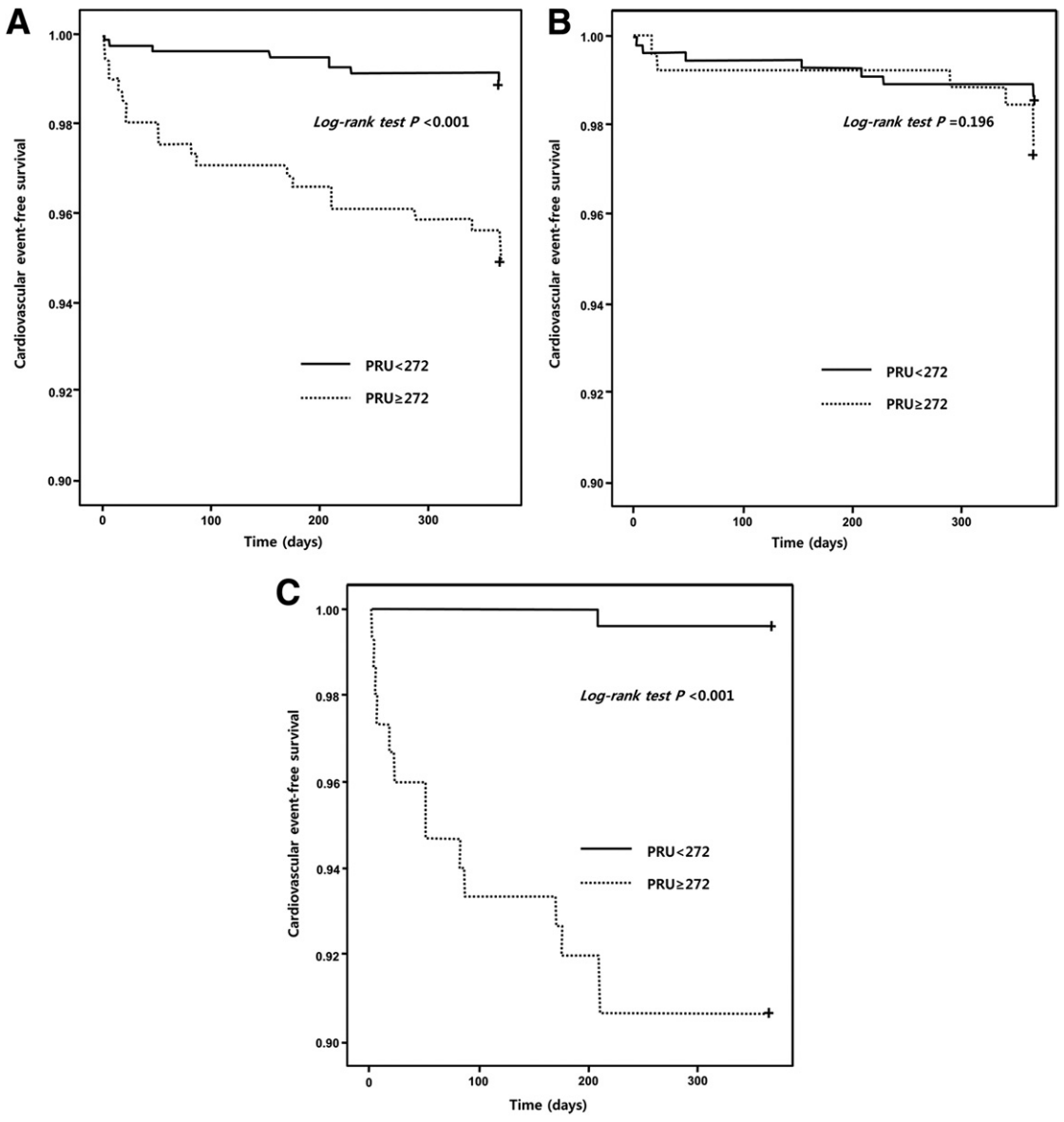

Figure 2. Survival Free From CV Death, Nonfatal MI, and Stent Thrombosis

(A) 1-year survival free from the combined endpoint of cardiovascular (CV) death, nonfatal myocardial infarction, or stent thrombosis was 94.9% in patients with HTPR and 98.9% in patients without HTPR in the overall population. **(B)** Among patients without AMI, no differences in event-free survival were found, according to the presence of HTPR. **(C)** Patients with AMI and HTPR had a higher prevalence of events than those without HTPR. PRU = $P2Y_{12}$ reaction unit; other abbreviations as in Figure 1.

Current methods to measure on-treatment platelet reactivity have several innate shortcomings for thrombotic risk stratification. First, they do not reflect total platelet reactivity; second, the soluble coagulation system in the plasma also is pivotal in the development of thrombosis (19,20). Third, much more than the effect of the antiplatelet agent is being measured. Fourth, in studies of platelet reactivity in individuals receiving no antiplatelet therapy, high reactivity has also correlated with worse outcomes (21,22). Therefore, a greater emphasis on platelet reactivity being a risk marker more than a guide for changing antiplatelet therapy would help better balance the clinical applicability of the results.

Studies using the VerifyNow P2Y12 assay have suggested that the optimal cutoffs of the PRU for low responsiveness to clopidogrel were between 230 and 240 (2,5–7). These cutoffs were based on the ROC analysis and corresponded well with the upper-tertile values. Conversely, the cutoff of the PRU for HTPR in the present study (≥272) was quite

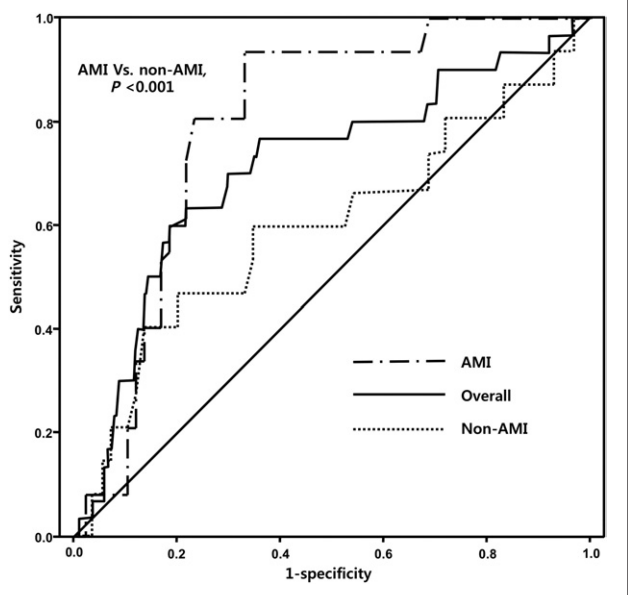

Figure 3. ROC Curve for the VerifyNow P2Y12 Assay

A receiver-operating characteristic (ROC) curve analysis of the $P2Y_{12}$ reaction unit could be used to distinguish between patients with and without post-discharge cardiovascular events (area under the curve: 0.708, 95% confidence interval [CI]: 0.607 to 0.809, $p < 0.001$). If divided between those with or without acute myocardial infarction (AMI), the area under the curve was larger in patients with AMI (0.792, 95% CI: 0.708 to 0.876, $p < 0.001$) compared with those without AMI (0.601, 95% CI: 0.433 to 0.769, $p = 0.180$).

high. Recent studies in Korean populations have also suggested a higher optimal cutoff for HTPR (10–12). Although we did not directly compare the responsiveness to clopidogrel between Korean populations and Caucasian populations, the higher cutoff for HTPR suggests that the response to clopidogrel decreased in Korean patients after PCI. Price et al. (23) reported that non-Caucasians had a higher PRU than Caucasians (229 vs. 200, $p = 0.041$), which is consistent with our results. This gap could be partially explained by inter-racial variability, a higher proportion of AMI in the study population (37.8%), and the timing of measurements after PCI. Inter-individual variability in the responsiveness to clopidogrel is well known (1), but data on inter-racial variability are unavailable. Recent genetic research on the polymorphism of cytochrome P450 (which is involved in the metabolism of the pro-drug clopidogrel into its active component) could provide a clue on inter-racial variability. Patients with *CYP2C19* loss of function alleles, which include *CYP2C19*2* and *CYP2C19*3*, have a higher PRU and worse outcome than non-carriers (24–26). The prevalence of *CYP2C19* loss of function varies considerably, depending on ethnicity. The frequency of the reduced-function variants of *CYP2C19* was much higher in the Asian population than in Caucasians (24,27). AMI is associated with heightened platelet reactivity. The higher proportion of AMI cases included is another possible explanation for the high HTPR cutoff in the present study. Price et al. (2) suggested an optimal cutoff of the PRU ≥235 in patients with approximately 93% stable angina or ischemia, and the GRAVITAS trial (which included only approximately 10.5% of AMI cases) suggested an optimal cutoff for HTPR ≥230 (7). The cutoff for HTPR in the present study was even higher, compared with that of a study comprising patients with acute coronary syndrome, including 28% of cases of ST-segment elevation MI (6).

There is no consensus with regard to the appropriate timing for the VerifyNow P2Y12 test. However, in most studies, the PRU was analyzed at ≥12 h after loading with 600 mg clopidogrel immediately before PCI or after PCI. The PCI itself could activate platelet reactivity, leading to a higher PRU value. Therefore, our higher PRU values might have been influenced by PCI itself, because we carried out the VerifyNow P2Y12 test 12 to 24 h after PCI. We did this because, in everyday practice, ad hoc PCI is done immediately after diagnostic coronary angiography in many patients and there are many emergency or urgent PCI cases. Therefore, there is not enough time to reach steady concentration of clopidogrel before PCI. Our PRU cutoff for HTPR seems to represent platelet reactivity integrating PCI and a given setting, such as AMI. Matetzky et al. (4) showed that post-clopidogrel platelet reactivity might change dynamically during the early phase of AMI and that it might stabilize from Day 3 to Day 5 after coronary stenting in AMI patients. This finding suggests that the appropriate sampling time for measurement of HTPR might be 3 to 5 days later in the AMI setting. A recent study by Campo et al. (28) claimed that the PRU measured 1 month after PCI might better predict post-discharge outcome. Thus, the optimal cutoff for HTPR should be determined after considering the chronology of the sample time with respect to PCI in different clinical conditions.

Study limitations. First, this is a single-center study in a Korean population. Second, genetic studies were lacking, so a hypothesis about the higher cutoff for HTPR could not be elucidated. Third, use of the VerifyNow P2Y12 assay might

Table 3. Predictors of Cardiovascular Events on Multivariate Cox Proportional Hazard Analysis

	Hazard Ratio	Confidence Interval	p Value
Female	2.692	0.984–7.187	0.054
AMI	2.397	0.996–5.688	0.051
EF <45%	2.679	1.057–6.792	0.038
Cr ≥1.5 mg/dl	4.719	1.285–17.327	0.019
HTPR ≥272 PRU	3.749	1.400–10.04	0.009

AMI = acute myocardial infarction; Cr = creatinine; EF = ejection fraction; HTPR = high on-treatment platelet reactivity; PRU = $P2Y_{12}$ reaction unit.

be associated with exclusion of higher-risk patients who received a glycoprotein IIb/IIIa inhibitor. Other tests, such as the vasodilator-stimulated phosphoprotein index might have been more adequate, because this test is not influenced by a glycoprotein IIb/IIIa inhibitor. However, the VerifyNow P2Y12 assay is a point-of-care and easier test than the vasodilator-stimulated phosphoprotein phosphorylation assay to assess HTPR. Fourth, a sizable proportion of approximately 40% of all AMI patients was considered to have high platelet reactivity, which diminishes the usefulness of HTPR as a long-term predictive test. Fifth, we did a single measurement of the PRU by the VerifyNow P2Y12 assay. In addition to interindividual variability, there is considerable intraindividual variability, and clopidogrel responsiveness seems to improve over time (3,28,29). Enhanced residual platelet reactivity does not seem to be a stable phenomenon, and a 1-month PRU might better predict adverse outcome (28). Repeat measurements might detect an increase or decrease in clopidogrel responsiveness (30) and improve the ability to distinguish patients with and without adverse clinical events.

Conclusions

Increased residual platelet reactivity was related to post-discharge CV events in subjects with AMI, whereas HTPR did not seem to predict outcome in patients with stable coronary diseases. The optimal cutoff of the PRU for HTPR in our Korean study cohort was higher than that of Caucasians. The different cutoff of the PRU for HTPR should be used according to a given clinical setting, ethnicity, and sampling time.

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Key Words: coronary angioplasty ■ drug effects ■ myocardial infarction ■ platelet activation ■ platelet function test.